REMARKS

Claims 1-28 and 30-39 are pending in this application. By this Amendment, claims 3, 4, 7, 9-13, 15-18, 21, 22, 25-28, and 30-35 are amended and claims 36-39 are added. Support for the amendments to the claims and new claims 36-39 may be found, for example, in the original claims. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Personal Interview

The courtesies extended to Applicants' representative by Examiner Whisenant at the interview held July 28, 2009, are appreciated. The reasons presented at the interview as warranting favorable action are incorporated into the remarks below, which constitute Applicants' record of the interview.

II. Written Description and Enablement Rejections

The Office Action rejects claim 25 under the written description and enablement requirements of 35 U.S.C. §112, first paragraph. Because both rejections are based in part on similar reasoning, Applicants address the rejections together, respectfully traversing the rejections for the following reasons.

Claim 25 is directed to "[a] method used in determining whether a patient is predisposed to a cancer or a genetic disease known to be associated or putatively associated with a specific point mutation, or used in diagnosing a patient suspected of suffering from said cancer or disease, or used in determining a prognosis of a patient diagnosed as having said cancer or disease" (emphasis added). By this Amendment, claim 25 requires the following steps (emphasis added):

> obtaining from the patient a nucleic acid suspected to include at least one mismatch corresponding to the specific point mutation;

> placing the nucleic acid, paired in duplex form, in a liquid medium and contacting the nucleic acid with at least one compound able to undergo a specific base pairing interaction with said mismatch, said at least one compound being used at a combined concentration of at least 10g/l in said medium; and
>
> assaying for said mismatch by an analytical method to detect whether said mismatch is present, wherein the presence of said mismatch indicates that the nucleic acid has the specific point mutation known to be associated or putatively associated with the cancer or the genetic disease.

As discussed and agreed upon during the interview, Applicants' disclosure supports and enables a basic method that can assay for the presence (or absence) of a mismatch in a strand of nucleic acids in duplex form (see claim 1). Nucleic acids, such as DNA and RNA, are all composed of the same chemically identical nucleotides. Thus, whether or not such nucleic acids are coding (e.g., a gene) or non-coding, or whether or not such nucleic acids are from an animal or plant, the nucleic acids can be assayed for a mismatch when in duplex form using the claimed method. Thus, from Applicants' disclosure, it would be readily apparent to those skilled in the art that the method of claim 1 is applicable to any experiment, protocol, method, analysis, etc., that includes looking for mismatches in duplexed nucleic acid molecules.

Also as discussed and agreed upon during the interview, numerous genetic point mutations that are associated with various types of cancers or other diseases are well-known in the art. Determining whether a patient has one or more of these point mutations that are known to be associated with a cancer or other disease is a valuable diagnostic or prognostic factor/indicator. It is well-known and common in the art to prescreen a patient for a certain mutation to determine if the patient is predisposed to a certain disease or condition. It is also well-known in the art that patients who are already ill and are suspected of having a certain condition may be tested for a certain mutation that is known to be associated with the suspected disease to confirm or aid in the diagnosis. It is also well-known in the art that

patients who are already diagnosed as having a certain cancer or other disease may be tested for certain mutations that are known prognostic indicators for the cancer or other disease.

In all of these "known" cases, the method of claim 1 has immediate applicability and is fully enabled. As an extension of this principle, claim 25 is fully enabled because it is directed to a method "used in determining whether a patient is predisposed to a cancer or a genetic disease known to be associated or putatively associated with a specific point mutation, or used in diagnosing a patient suspected of suffering from said cancer or disease, or used in determining a prognosis of a patient diagnosed as having said cancer or disease."

As to the Office Action's concern about the claim encompassing mutations associated with a cancer or genetic disease not yet discovered, the language of claim 25 requires that the cancer or genetic disease is "known to be associated or putatively associated with a specific point mutation" (emphasis added). One of skill in the art would readily appreciate that the claimed method would be immediately applicable and enabled as soon as a yet-to-be discovered mutation is known to be associated with a specific condition.

The inventive methods disclosed in this application have broad and general applicability to any nucleic acid that can exist in duplex form. Whether a subject nucleic acid is from organism x or y, or whether it is coding or non-coding, or whether it is suspected of having a mutation associated with disease a or b is immaterial to the methods' ability to detect mismatches. In other words, the ability of the method to detect mismatches is not dependent on the nucleic acid. This is very different from the theoretical scenario discussed in *Univ. of Rochester* as quoted on pages 3–4 of the Office Action, where the claimed method for curing cancer was solely dependent upon a compound that attacks and destroys cancer cells while leaving healthy cells alone, but there was no possession of such a compound.

Possession of the method of claim 1 and its use and applicability in the context set forth in claim 25 is evident from the original disclosure. The Office Action's concerns that

Applicant has not identified the probes/primers/target nucleotide sequences are believed to be sufficiently addressed by the amendments made to claim 25 and the above remarks.

The method of claim 25 is also enabled for its full scope. The Office Action's concern that the method does not set forth a prognosis for a given individual is believed to be sufficiently addressed by the amendments made to claim 25. Specifically, the claim method recites open claim language ("comprising") and is to be "used in determining a prognosis of a patient diagnosed as having said cancer or disease" (emphasis added).

Thus, the claimed method does not preclude nor does it have to be a complete substitute for the various other factors that a medical professional would take into consideration when making a prognosis or diagnosis. Instead, the results obtained from the claimed method--an indication of whether a patient has a specific point mutation that corresponds to a genetic disease or cancer--may be factored in by a medical professional with other factors such as age, gender, medical condition, medical history, etc. in arriving at a prognosis or diagnosis. Thus, the claimed method can be used as an informative prognostic/diagnostic tool, and an ordinarily skilled artisan would readily understand how to the practice the claimed method as such.

For at least these reasons, claim 25 meets the written description and enablement requirements. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

IV. Rejection Under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 12, 13, and 25 under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully traverse the rejection.

By this Amendment, claims 12 and 25 are amended to overcome the rejection. With respect to claim 12, and as discussed during the interview, claim 9 is directed to a compound able to undergo a specific pairing interaction with a mismatch that is "selected from the group

consisting of oligonucleotides less than 5 nucleotides in length, nucleosides, bases, and mixtures thereof." Claim 12 further requires that "the oligonucleotides less than 5 nucleotides in length, the nucleosides, the bases, and the mixture thereof are unable to undergo base pairing interactions with each other" (emphasis added), which does not affect the ability of the compound to undergo a specific pairing interaction with a mismatch in a strand of nucleic acids paired in duplex form.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

V. Rejections Under 35 U.S.C. §102

A. Saiki

The Office Action rejects claims 32, 34, and 35 under 35 U.S.C. §102(b) as being anticipated by "Analysis of Enzymatically Amplified β-globin and HLA-DQα DNA with Allele-Specific Oligonucleotide Probes" by Saiki et al. ("Saiki"). Applicants respectfully traverse the rejection.

By this Amendment, claims 32 and 34 are amended to require "a compound able to undergo specific base pairing interaction at a concentration of at least 10 g/l" (emphasis added) and "a pool of compounds able to undergo specific base pairing interaction with nucleotides and/or nucleotide analogues . . . at a combined concentration of at least 10 g/l" (emphasis added), respectively. Saiki fails to disclose the claimed concentration.

The Office Action asserts that Saiki discloses a reaction mixture having dNTPs at a combined concentration of 3.347 g/l based on each dNTP being present in a concentration of 1.5 mM. See Office Action at page 9. As discussed and agreed upon during the interview, Saiki does not disclose a concentration of at least 10 g/l.

Thus, Saiki does not anticipate claims 32 and 34. Claim 35 depends from claim 34 and, thus, also is not anticipated by Saiki for at least the same reason. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Fisher

The Office Action rejects claims 27, 28, and 31-33 under 35 U.S.C. §102(a) as being anticipated by Fisher BioReagents' "ex CTGene™ PCR Kits" ("Fisher"). Applicants respectfully traverse the rejection.

1. Claim 27

By this Amendment, claim 27 is amended to require "a compound able to undergo specific base pairing interaction at a concentration of at least 1 g/l being present in a liquid separating medium that comprises at least one polymer at a concentration of at least 1% by weight" (emphasis added). Fisher does not disclose a liquid separating medium comprising a polymer.

Instead, Fisher discloses a PCR nucleotide mix (10 mM) in a buffer. The Office Action asserts that this buffer is equivalent to a liquid separating medium. See page 9. However, as discussed and agreed upon during the interview, Fisher does not disclose a buffer comprising a polymer. Thus, Fisher does not disclose each and every element of claim 27.

2. Claims 31 and 32

Claims 31 and 32 are directed to a composition that comprises (1) "a compound able to undergo specific base pairing interaction at a concentration of at least 10 g/l," and (2) "a DNA fragment having a nucleic sequence related to a gene on which point mutation(s) has been associated or putatively associated with a disease or an increased predisposition to a disease" (claim 31) or "a pair of DNA probes" (claim 32). Fisher does not disclose this combination of features for at least the following reasons.

Fisher discloses the following three compositions: (1) a PCR nucleotide mix (10 mM) in a buffer, (2) control DNA template (1 ng/μg) in a buffer, and (3) a control primer (20 μm) in a buffer (i.e., Control Primers 1, 2, and 3). None of compositions (1)-(3) comprise both a compound able to undergo specific base pairing interaction at a concentration of at least 10 g/l and DNA. Additionally, the control DNA template and Control Primers 1, 2, and 3 are not "a DNA fragment having a nucleic sequence related to a gene on which point mutation(s) has been associated or putatively associated with a disease or an increased predisposition to a disease" (claim 31).

When mixed into a single reaction mixture, compositions (1)-(3) are present at concentrations that are different from their "stock" solutions. Accordingly, in the reaction mixture, the PCR nucleotides (dNTPs) would not be present at a concentration of 10 mM, but at a much lower concentration. As evidence, Saiki discloses a PCR reaction in which the reaction buffer comprises each dNTP at a concentration of 1.5 mM. See Figure 2 at legend. The Office Action asserts that each dNTP at this concentration equals a combined concentration of 3.347 g/l for all dNTPs. See page 9. Thus, Fisher does not disclose a composition comprising the combination of claimed compound at a concentration of at least 10 g/l and a DNA fragment or DNA probes. Accordingly, Fisher does not disclose each and every element of claims 31 and 32.

3. Conclusion

For at least these reasons, Fisher does not anticipate claims 27, 31, and 32. Claims 28 and 33 depend from claim 27 and, thus, also are not anticipated by Fisher for at least the same reasons discussed above with respect to claim 27. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

VI. Rejections Under 35 U.S.C. §103

A. Fishel

The Office Action rejects claims 1-4, 6-10, 14-18, 25, and 26 under 35 U.S.C. §103(a) as having been obvious over WO 99/10369 to Fishel et al. ("Fishel"). Applicants respectfully traverse the rejection.

Claims 1, 3, and 25 require at least one compound able to undergo a specific base pairing interaction with a mismatch at a combined concentration of 10 g/l. Fishel would not have rendered obvious a method using this compound at the claimed concentration for at least the following reasons.

Fishel discloses a method of modifying mismatched duplex DNA that comprises contacting a MutS homolog ("MSH") dimer and the mismatched duplex DNA in the presence of a binding solution that comprises at least one of ADP and ATP, where ATP is present at a concentration of less than about 3 μm. See page 6, lines 17-22. Fishel discloses that gel shift assays were performed by incubating an MSH heterodimer with labeled substrate DNA (9 x 10^{-15} moles) that is mismatched or not mismatched in a buffer that includes poly dI-dC DNA (10 ng/μl). See page 58, line 22 to page 59, line 12 ("Gel mobility shift assays"). The Office Action asserts that poly dI-dC DNA is a compound able to undergo a specific base pairing interaction with a mismatch and that an ordinarily skilled artisan performing routine optimization would have modified the gel shift assay of Fishel to include poly dI-dC DNA at the claimed concentration. See page 10.

However, poly dI-dC, which is a perfectly complementary double-stranded DNA, cannot base pair to a mismatch because all nucleotides of poly dI-dC are already base paired. Instead, poly dI-dC is present in the reaction mixture of a gel shift assay to provide a substrate for non-specific binding of proteins that are not of interest, preventing an unacceptable level of non-specific binding of proteins on the DNA substrate under investigation (e.g., a

mismatched DNA substrate). If poly dI-dC DNA is base paired with a DNA substrate having a mismatch, it would have rendered the gel shift assay of Fishel unsatisfactory for its intended purpose because it would have prevented binding of the MSH heterodimer to the mismatched DNA.

Additionally, the claimed concentration of 10 g/l is a thousand (1000) times greater than the concentration of poly dI-dC DNA used in Fishel's gel shift assay. An ordinarily skilled artisan would not have modified Fishel's gel shift assay to use poly dI-dC at a 1000 times the disclosed concentration because doing so would have increased the cost of performing the assay unless the assay would be improved in some manner that would offset the increase in cost.

However, the ordinarily skill artisan would not have expected that greatly increasing the concentration of poly dI-dC would improve the assay, but instead would have expected that it would have rendered the assay unsatisfactory for its intended purpose. See MPEP §2142.01(V) (modifying the prior art cannot render it unsatisfactory for its intended purpose). Increasing the concentration of poly dI-dC 1000 fold would have been expected to interfere with the binding of the MSH heterodimer to the mismatched DNA because any non-specific binding between the MSH heterodimer and poly dI-dC would have been expected to correspondingly increase. Thus, poly dI-dC would have been expected to compete against and, perhaps, out-compete the mismatched DNA for binding of the MSH heterodimer. Thus, an ordinarily skilled artisan would not have increased the concentration of poly dI-dC to at least 10 g/l in Fishel's gel shift assay on the basis of routine optimization.

The Office Action also improperly relies on Applicants' disclosure in asserting that the claimed concentration would have been arrived at by an ordinarily skilled artisan through routine optimization. See page 10. Specifically, the Office Action cites to the specification and asserts that Applicants disclose preferred ranges that encompass any value above a

threshold and improperly concludes that such broad ranges are evidence of routine optimization. Id. This analysis is based solely on Applicants' disclosure and not the prior art and, thus, renders the Office Action's determination of obviousness improper. Moreover, as discussed in the specification, an unexpected feature "is that the compounds able of specific base pairing interactions with the nucleic acids to be tested, are used with best performances at much higher concentrations, as generally used for base-pairing compounds in the prior art" (emphasis added). See page 14, lines 12-15. This is indicative of inventiveness and not routine optimization.

For at least these reasons, Fishel would not have rendered obvious claims 1, 3, and 25. Claims 2, 4, 6-10, 14-18, and 26 variously depend from claims 1, 3, and 25 and, thus, also would not have been rendered obvious by Fishel for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Fishel, Righetti, and Vivoy

The Office Action rejects claims 19-24 under 35 U.S.C. §103(a) as having been obvious over the combination of Fishel and "Analysis of Nucleic Acids by Capillary Electrophoresis" by Righetti et al. ("Righetti) and/or "Advanced Polymers for DNA Seperation" by V. Barbier and J. Viovy ("Viovy"). Applicants respectfully traverse the rejection.

Claims 19-24 variously depend from claim 1 and, therefore, contain all the features of claim 1. The deficiencies of Fishel with respect to claim 1 are discussed above. Righetti and Viovy, which are applied by the Office Action for the additional features recited in claims 19-24, do not cure the deficiencies of Fishel with respect to claim 1.

Thus, the combination of applied references would not have rendered obvious claims 19-24. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Fisher and Righetti

The Office Action rejects claim 30 under 35 U.S.C. §103(a) as having been obvious over the combination of Fisher and Righetti. To the extent that the rejection is also deemed to apply to amended claim 27, Applicants respectfully traverse the rejection as to claims 27 and 30 for the following reasons.

By this Amendment, claim 27 is amended to be directed to "[a] composition comprising a compound able to undergo specific base pairing interaction at a concentration of at least 1 g/l being present in a liquid separating medium that comprises at least one polymer at a concentration of at least 1% by weight" (emphasis added) As discussed above and agreed upon during the interview, Fisher does not disclose a liquid separating medium comprising a polymer. The Office Action asserts that Righetti teaches a liquid separating medium comprising a sieving polymer and that it would have been obvious to include a liquid separating medium comprising a sieving polymer as a reagent in the kit disclosed by Fisher. See page 12. Without conceding the propriety of this assertion, it would not have been obvious to provide a compound able to undergo specific base pairing interaction at the claimed concentration in the sieving medium of Righetti (see page 265) and the Office Action does not assert otherwise.

Thus, Fisher and Righetti would not have rendered obvious claim 27. Claim 30 depends from claim 27 and, thus, also would not have been rendered obvious by the applied references for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

D. Pastinen

The Office Action rejects claims 1, 2, 5, 8-11, and 25 under 35 U.S.C. §103(a) as having been obvious over "Minisequencing: A Specific Tool for DNA Analysis and

Diagnostics on Oligonucleotide Arrays" by Pastinen et al. ("Pastinen"). Applicants respectfully traverse the rejection.

1. **Claims 1, 5, and 25**

Claims 1, 5, and 25 require at least one compound able to undergo a specific base pairing interaction with a mismatch at a combined concentration of 1 g/l (claim 5) or 10 g/l (claims 1 and 25). Pastinen would not have rendered obvious a method using this compound at the claimed concentration for at least the following reasons.

Pastinen discloses a microsequencing reaction in which the reaction mixtures contain 0.2 pmole of the appropriate labeled ddNTP and 0.2 pmole of the other three unlabeled ddNTPs. See page 613, left column, lines 5-13. The Office Action asserts that that an ordinarily skilled artisan performing routine optimization would have modified the microsequencing reaction of Pastinen to include the ddNTPs at the claimed concentration. See page 13.

However, the claimed concentration of at least 1 g/l (claim 5) and 10 g/l (claims 1 and 25) is 2.5×10^{11} and 2.5×10^{12}-fold greater, respectively, than the concentration of ddNTPs disclosed by Pastinen for its microsequencing reaction. An ordinarily skilled artisan would not have modified Pastinen's microsequencing reaction to use ddNTPs at a much greater concentration than the disclosed concentration because doing so would have unnecessarily increased the cost of performing the microsequencing reaction.

Additionally, modifying Pastinen's microsequencing reaction as proposed would have rendered it unsatisfactory for its intended purpose. See MPEP §2142.01(V). During the microsequencing reaction, ddNTPs act to "stop" the extension of the immobilized primers bound to the template sequences. The reaction is dependent on the concentration of ddNTPs because sequencing requires that the primers are randomly and variously extended for some length before a ddNTP is incorporated into the extension product, terminating extension.

Thus, a large increase in the amount of such "stop" nucleotides would prevent any meaningful extension, destroying the usefulness of the microsequencing reaction because extension products of varying length are required for providing sequencing data.

Thus, the proposed modification would have rendered Pastinen's microsequencing reaction unsatisfactory for its intended purpose. Moreover, as discussed above with respect to Fishel, the Office Action also improperly relies on Applicants' disclosure as a basis for determining obviousness. Thus, Pastinen would not have rendered obvious claims 1, 5, and 25.

2. Claim 11

Claim 11 depends from claim 1 and, thus, also would not have been rendered obvious by Pastinen for at least the reasons discussed above. Additionally, claim 11 requires that " the compound is selected from the group consisting of adenosine, guanosine, uridine, cytidine, thymidine, and mixtures thereof." Pastinen does not disclose these nucleosides.

Pastinen discloses nucleotides, such as dNTPs and ddNTPs. Nucleotides consist of a sugar, a base, and a phosphate group. On the other hand, nucleosides consist of a sugar and a base, but do not contain a phosphate group. Thus, nucleosides are unable to be incorporated into an extension product by a polymerase because without a phosphate group they cannot form phosphodiester bonds. Because nucleosides cannot be incorporated into an extension product, an ordinarily skilled artisan would not have included them in Pastinen's reaction mixture because there was no reason to believe that they would have performed any function whatsoever.

3. Conclusion

For at least these reasons, Pastinen would not have rendered obvious claims 1, 5, 11 and 25. Claims 2 and 8-10 variously depend from claim 1 and, thus, also would not have been rendered obvious by Pastinen for at least the same reasons discussed above with respect

to claim 1. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

VII. New Claims

By this Amendment, new claims 36-39 are presented. New claim 36 depends from claim 25 and, thus, distinguishes over the Pastinen for at least the same reasons discussed above with respect to claim 25. New process claims 37-39 are patterned off of composition claims 27, 31, and 32, respectively, and, thus, distinguish over the applied references for reasons similar to those discussed above with respect to claims 27, 31, and 32, as well as for the reason that each claim is directed to "[a] method for assaying for the presence of a mismatch on a nucleic acid in duplex form." Accordingly, prompt examination and allowance of new claims 36-39 are respectfully requested.

VIII. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of this application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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WPB:MCB

Attachments:
Petition for Extension of Time
Amendment Transmittal

Date: September 8, 2009

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